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REVIEW ARTICLE

Anti-inflammatory therapies in myocardial infarction: failures, hopes and challenges

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In the infarcted heart, the damage-associated molecular pattern proteins released by necrotic cells trigger both myocardial and systemic inflammatory responses. Induction of chemokines and cytokines and up-regulation of endothelial adhesion molecules mediate leukocyte recruitment in the infarcted myocardium. Inflammatory cells clear the infarct of dead cells and matrix debris and activate repair by myofibroblasts and vascular cells, but may also contribute to adverse fibrotic remodelling of viable segments, accentuate cardiomyocyte apoptosis and exert arrhythmogenic actions. Excessive, prolonged and dysregulated inflammation has been implicated in the pathogenesis of complications and may be involved in the development of heart failure following infarction. Studies in animal models of myocardial infarction (MI) have suggested the effectiveness of pharmacological interventions targeting the inflammatory response. This article provides a brief overview of the cell biology of the post-infarction inflammatory response and discusses the use of pharmacological interventions targeting inflammation following infarction. Therapy with broad anti-inflammatory and immunomodulatory agents may also inhibit important repair pathways, thus exerting detrimental actions in patients with MI. Extensive experimental evidence suggests that targeting specific inflammatory signals, such as the complement cascade, chemokines, cytokines, proteases, selectins and leukocyte integrins, may hold promise. However, clinical translation has proved challenging. Targeting IL-1 may benefit patients with exaggerated post-MI inflammatory responses following infarction, not only by attenuating adverse remodelling but also by stabilizing the atherosclerotic plaque and by inhibiting arrhythmia generation. Identification of the therapeutic window for specific interventions and pathophysiological stratification of MI patients using inflammatory biomarkers and imaging strategies are critical for optimal therapeutic design.

Abbreviations

11β-HSD, 11-β hydroxysteroid dehydrogenase; ACS, acute coronary syndrome; CRP, C-reactive protein; ECM, extracellular matrix; GR, glucocorticoid receptor; iNKT, invariant natural killer T cells; IRAK, IL-1 receptor associated kinase; MI, myocardial infarction; MR, mineralocorticoid receptor; NSAIDs, nonsteroidal anti-inflammatory drugs; PCI, percutaneous coronary intervention; SDF, stromal cell-derived factor; STEMI, ST elevation myocardial infarction; Tregs, regulatory T cells; α-SMA, α-smooth muscle actin

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Introduction

Myocardial infarction (MI) is a major cause of morbidity and mortality worldwide. Implementation of reperfusion strategies in patients presenting with ST elevation MI (STEMI) has significantly reduced acute mortality. However, this remarkable therapeutic success resulted in an expansion of the pool of patients who, while surviving the acute event, remain at risk for development of heart failure. The pathogenesis of heart failure following MI is intricately linked with repair and remodelling of the infarcted heart. The term 'post-infarction ventricular remodelling' describes a constellation of cellular, molecular and proteomic changes in both infarcted and non-infarcted myocardium that ultimately result in chamber dilation, hypertrophy of viable segments and progressive myocardial dysfunction. In human patients, dilative remodelling of the ventricle is associated with higher mortality and increased incidence of ventricular arrhythmias. The severity of adverse post-infarction remodelling is dependent on the size of the infarct but is also affected by the qualitative characteristics of cardiac repair and by the profile of cellular and molecular alterations in the viable myocardium.

Extensive experimental evidence suggests that MI is intricately associated with activation of an inflammatory reaction (Frangogiannis, 2014a). Inflammatory mediators are directly involved in the pathogenesis of the vulnerable plaque, leading to occlusion of the coronary vessel and subsequent necrosis of the myocardial territory served by the vessel. Cardiomyocyte necrosis triggers both a systemic inflammatory response, mobilizing bone marrow-derived immune cells, and a local reaction, leading to recruitment of circulating inflammatory cells that serve to clear the infarct from dead cells and matrix debris. Although leukocyte subsets play an important role in repair of the infarcted heart, prolonged activation of inflammatory pathways is involved in chronic adverse remodelling of the ventricle. Despite an impressive growth in our understanding of the role of inflammation in the pathogenesis of coronary occlusion and in the pathophysiology of cardiac repair remodelling and fibrosis, development of therapeutic strategies targeting inflammatory signals in patients with MI poses major challenges. This review provides a brief overview of the role of inflammatory cascades in injury, repair and remodelling of the infarcted heart, describes the long history of failed attempts to attenuate post-ischaemic dysfunction and to reduce adverse remodelling by targeting inflammation, and discusses promising new therapeutic approaches and the challenges of clinical implementation.

The role of inflammation in plaque rupture

In patients, ruptured atherosclerotic plaques are responsible for the majority of cases of fatal MI (Davies and Thomas, 1984). Both systemic inflammation and local activation of macrophage-driven inflammatory signalling in the microenvironment of the plaque have been implicated in the pathogenesis of plaque rupture (Crea and Libby, 2017). Induction of chemokines, such as **CCL2** and **fractalkine/CX3CL1**, mediate recruitment of macrophages in atherosclerotic plaques (Gu *et al.,* 1998; Lesnik *et al.,* 2003). The diverse phenotypic profiles of macrophages critically regulate progression, evolution and even regression of the atherosclerotic process (Mantovani *et al.,* 2009; Rahman *et al.,* 2017). **Angiotensin II** (Schieffer *et al.,* 2000), oxidized LDL (Xu *et al.,* 1999), **CD40** signalling (Mach *et al.,* 1997) and pro-inflammatory cytokines stimulate macrophage-derived expression of proteases (including **MMPs** and cathepsins), degrading the extracellular matrix (ECM) of the fibrous cap (Shah *et al.,* 1995) and promoting plaque fissuring. Moreover, local release of cholesterol crystals activates the inflammasome, generating active **IL-1β** and triggering pro-inflammatory signalling (Freigang *et al.,* 2011). In addition to the direct actions of pro-inflammatory mediators on macrophage phenotype, mast cell degranulation, dysregulation of T cell subsets, B-cell-derived cytokine synthesis and stimulation of vascular cells in the plaque environment have also been implicated in activation of inflammatory macrophages in atherosclerotic plaques (Kaartinen *et al.,* 1996; Mazzolai *et al.,* 2004; Tay *et al.,* 2016; Sage and Mallat, 2017; Tabas and Lichtman, 2017).

Activation of the post-infarction inflammatory response

Prolonged coronary occlusion leads to death of the cardiomyocytes in the tissues served by the vessel, triggering activation of an intense inflammatory reaction. The post-infarction inflammatory response can be divided in three phases: the alarm phase characterized by release of damage-associated molecular pattern (DAMP) proteins that stimulate innate immune pathways; the leukocyte mobilization phase, marked by recruitment of neutrophils, monocytes and lymphocytes in the infarcted area; and the resolution phase, associated with suppression of pro-inflammatory signalling and clearance of the leukocyte infiltrate (Figure 1).

During the alarm phase, necrotic cardiomyocytes release danger signals (such as high mobility group box-1, **heat shock proteins**, **adenosine**, extracellular RNA, and **IL-1α**) that stimulate innate immune signalling (Andrassy *et al.,* 2008; Chen *et al.,* 2014; Lugrin *et al.,* 2015). Generation of ECM fragments also contributes to the intense inflammatory reaction in the infarcted area (Huebener *et al.,* 2008). Stimulation of innate immune responses following infarction involves effects of alarmins on **Toll-like receptor** and **receptor for advanced glycation end-products**-dependent pathways in leukocytes, vascular cells and fibroblasts triggering transcription of pro-inflammatory cytokines and chemokines (Arslan *et al.,* 2011a; Zhang *et al.,* 2015). Activation of the complement cascade also contributes to the post-infarction inflammatory response (Hill and Ward, 1971; De Hoog *et al.,* 2014). Post-infarction inflammation not only serves to clear dead cells and matrix debris from the infarcted tissue but also sets the stage for repair of the infarcted area. In addition to activation of a local myocardial inflammatory response, infarction also triggers systemic inflammation, stimulating release of bone marrow-derived leukocytes. In mouse models of MI, the spleen has also been suggested as an

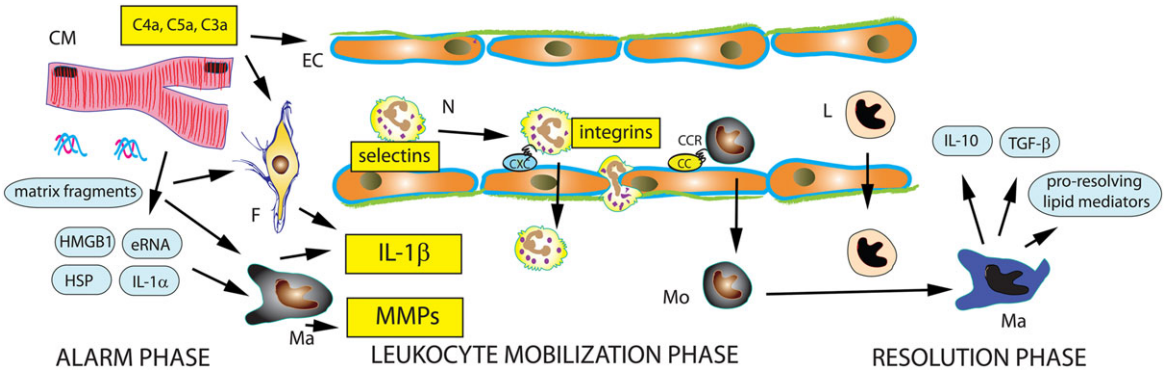

Figure 1

The inflammatory response following MI can be divided into three phases: the alarm phase, the leukocyte mobilization phase and the resolution phase. Necrotic cardiomyocytes (CM) release alarmins (heat shock proteins [HSP], high mobility group box 1 [HMGB1], extracellular RNA/eRNA, IL-1α and other danger signals) that activate innate immune signalling pathways. ECM fragments also trigger inflammatory signalling. Induction of pro-inflammatory cytokines, such as IL-1, and chemokines mediates recruitment of neutrophils (N) and pro-inflammatory monocytes (Mo) through interactions with endothelial cells (EC) that involve selectins and integrins. Clearance of dead cells and matrix debris from the infarct triggers transition to the resolution phase. Anti-inflammatory lymphocyte (L) and macrophage (Ma) subsets release mediators that suppress pro-inflammatory signalling, such as IL-10, TGF-β and pro-resolving lipid mediators. Experimental studies suggest that inhibition of the complement cascade, IL-1β antagonism, CCL2 inhibition, selectin and leukocyte integrin neutralization may be promising therapeutic strategies for patients with MI. F, fibroblast.

important contributor of inflammatory leukocytes (Swirski *et al.*, 2009). Although the relative role of the cardio-splenic axis in human MI remains unclear, clinical investigations have suggested that patients with acute coronary syndromes (ACS) have increased splenic metabolic activity and that activation of the spleen independently predicts cardiovascular events (Emami *et al.*, 2015).

The cytokines and chemokines

Induction of pro-inflammatory cytokines is a hallmark of the post-infarction inflammatory response. Early release of **TNF-α** (Frangogiannis *et al.*, 1998) triggers a cytokine cascade that mediates recruitment of leukocytes in the infarcted myocardium. Activation of the inflammasome platform in fibroblasts, cardiomyocytes and immune cells (Kawaguchi *et al.*, 2011; Mezzaroma *et al.*, 2011) stimulates release of active IL-1β, a critical mediator in regulation of cardiac inflammation and repair. IL-1 signalling stimulates chemokine synthesis and promotes leukocyte infiltration in the infarcted myocardium (Bujak *et al.*, 2008). Cardiac fibroblasts also respond to IL-1, by acquiring a pro-inflammatory and matrix-degrading phenotype and by secreting cytokines, chemokines and MMPs. Moreover, IL-1 delays myofibroblast conversion, suppressing synthesis of α-smooth muscle actin (α-SMA) (Saxena *et al.*, 2013). The effects of IL-1 on cardiac fibroblasts may serve to prevent premature acquisition of a matrix-synthetic phenotype, until the infarct is cleared of dead cells and matrix debris.

Chemokines are also markedly up-regulated in the infarcted heart and have been demonstrated to mediate leukocyte recruitment. Induction of both CXC and CC chemokines has been consistently demonstrated in experimental models of MI. CXC chemokines containing the ELR motif (Glu-Leu-Arg), such as **CXCL8/IL-8**, have been implicated in neutrophil recruitment (Ivey *et al.*, 1995). On the other hand, members of the CC chemokine subfamily, such as CCL2 and **CCL7**, mediate recruitment of pro-inflammatory monocytes (Dewald *et al.*, 2005; Nahrendorf *et al.*, 2007; Zouggari *et al.*, 2013). Some members of the chemokine family may have effects on non-haematopoietic cells, such as cardiomyocytes, fibroblasts and vascular cells. The CXC chemokine **SDF-1/CXCL12** may recruit progenitor cells with angiogenic potential (Liehn *et al.*, 2011), contributing to neovascularization of the scar, and may stimulate pro-survival cascades in ischaemic cardiomyocytes (Aiuti *et al.*, 1997; Askari *et al.*, 2003). The CXC chemokine **IP-10/CXCL10** is markedly up-regulated in experimental models of MI and may suppress fibrosis by inhibiting growth factor-mediated fibroblast migration (Bujak *et al.*, 2009; Saxena *et al.*, 2014a).

Recruitment of leukocytes

Chemokines and cytokines play a critical role in recruitment of inflammatory leukocytes in the infarcted myocardium. Cytokine-mediated induction of adhesion molecules in endothelial cells and integrin activation in leukocytes trigger adhesive interactions, ultimately leading to neutrophil, monocyte and lymphocyte extravasation in the infarcted area (Yamazaki *et al.*, 1993; Frangogiannis, 2014a). Leukocyte subpopulations have been suggested to play important roles in both injurious and repair processes following MI. Early studies suggested that infiltrating neutrophils may extend ischaemic injury by exerting cytotoxic effects on viable cardiomyocytes in the infarct border zone (Entman *et al.*, 1992). On the other hand, neutrophils have been suggested to orchestrate repair of the infarcted heart by modulating macrophage phenotype (Horckmans *et al.*, 2017).

The macrophages

Monocytes recruited to the infarct region differentiate into macrophages and phagocytose dead cells and matrix debris, while secreting cytokines and growth factors that orchestrate repair. Clearance of apoptotic cells by professional phagocytes, a process known as efferocytosis (Wan *et al.,* 2013), triggers cascades that suppress inflammation and promote activation of reparative mesenchymal cells. Ingestion of apoptotic cells is associated with release of anti-inflammatory cytokines, such as **IL-10** and **TGF-β** (Huynh *et al.,* 2002), suppressing inflammation and activating a fibrogenic and matrix-preserving programme. Several lines of evidence suggest crucial protective actions of macrophages in cardiac repair. First, macrophage depletion increased adverse remodelling in infarcted mice (van Amerongen *et al.,* 2007). Second, in experimental models, macrophages played a crucial role in preventing mural thrombus formation following MI (Ben-Mordechai *et al.,* 2013; Frantz *et al.,* 2013). Third, generation of alternatively activated macrophages exhibiting an M2-like phenotype is critical to protect the infarcted heart from cardiac rupture (Shiraishi *et al.,* 2016). Transition of macrophages into an anti-inflammatory phenotype may also require activation of intracellular inhibitory cascades that restrain the immune response, such as expression of **IL-1 receptor associated kinase (IRAK)-M**, an inhibitory member of the IRAK family that suppresses innate immune signalling (Chen *et al.,* 2012). It has been suggested that therapeutic activation of the reparative properties of macrophages through administration of **IL-4** may exert protective actions in acute MI (Shintani *et al.,* 2017). However, such therapeutic approaches need to be cautiously implemented, considering the known pro-fibrotic actions of IL-4 in the remodelling heart (Peng *et al.,* 2015).

The lymphocytes

Early infiltration of the infarcted heart with lymphocyte subsets has been extensively documented in experimental models of MI (Frangogiannis *et al.,* 2000a; Yan *et al.,* 2013). Moreover, clinical studies have suggested that effector T cells may be trapped in the coronary microcirculation following reperfusion of the infarcted area and may contribute to the pathogenesis of microvascular obstruction, extending ischaemic cardiomyocyte injury (Boag *et al.,* 2015). Early recruitment of lymphocyte subpopulations to the infarcted myocardium has been suggested to stimulate neutrophil and monocyte infiltration. B cells have been demonstrated to promote mobilization of pro-inflammatory monocytes, thus playing a central role in activation of the inflammatory cascade (Zouggari *et al.,* 2013). $CD4^{-}\gamma\delta$T-cells have been implicated in neutrophil and macrophage infiltration and may promote adverse remodelling following MI (Yan *et al.,* 2012). It should be emphasized that other lymphocyte subsets, such as regulatory T cells (Tregs), CD4+ helper T cells and invariant natural killer T (iNKT) cells, may have important repair functions following MI, negatively regulating inflammation, and activating mesenchymal and angiogenic cell populations to limit adverse remodelling (Dobaczewski *et al.,* 2010; Hofmann *et al.,* 2012; Sobirin *et al.,* 2012; Weirather *et al.,* 2014; Saxena *et al.,* 2014b).

Negative regulation of the post-infarction inflammatory response

Although macrophages are key effector cells in suppression of the post-infarction inflammatory response, several other cell types may contribute to downmodulation of pro-inflammatory signalling. Anti-inflammatory lymphocyte subsets, such as Tregs (Dobaczewski *et al.,* 2010; Weirather *et al.,* 2014; Saxena *et al.,* 2014b), iNKT cells (Sobirin *et al.,* 2012) and dendritic cells (Anzai *et al.,* 2012) have been identified as important sources of anti-inflammatory cytokines in the healing infarct. Surviving cardiomyocytes in the infarct border zone may also limit and restrain inflammation by secreting mediators that recruit and activate regulatory and reparative macrophages (Lorchner *et al.,* 2015). Acquisition of an anti-inflammatory phenotype by vascular cells may also contribute to negative regulation of post-infarction inflammation. Members of the TGF-β family may inhibit adhesion molecule expression by endothelial cells and leukocytes, inhibiting leukocyte-endothelial cell interactions and preventing uncontrolled leukocyte recruitment (Kempf *et al.,* 2011). Recruitment of mural cells by infarct neovessels may serve to suppress endothelial pro-inflammatory activation (Zymek *et al.,* 2006). Thus, timely suppression and spatial containment of the inflammatory response following infarction is dependent on activation of a wide range of molecular signals with actions on several different cell types. In animal models, defects in these regulatory mechanisms result in unrestrained, prolonged or expanded inflammation, leading to accentuated cardiac remodelling and worse dysfunction following infarction. In patients, defective negative regulation of the post-infarction inflammatory response may be involved in the pathogenesis of adverse remodelling and heart failure in patients surviving an acute MI (Frangogiannis, 2014a).

Myofibroblast activation

Because the adult mammalian heart has negligible regenerative capacity, repair of the infarcted myocardium is dependent on fibroblast activation and subsequent formation of a collagen-based scar. Perturbations in fibroblast activation and in the profile of ECM proteins in the infarcted and remodelling myocardium can be associated with increased dysfunction and adverse remodelling (Frangogiannis *et al.,* 2005; Kong *et al.,* 2017). During the proliferative phase of infarct healing, the cardiac fibroblast population markedly expands (Frangogiannis *et al.,* 2000b). Activated myofibroblasts form organized arrays in the infarct border zone (Blankesteijn *et al.,* 1997). These cells incorporate into their cytoskeleton contractile proteins (such as α-SMA and the embryonal isoform of smooth muscle myosin) (Willems *et al.,* 1994; Frangogiannis *et al.,* 2000b; Shinde *et al.,* 2017) but do not express markers of mature vascular smooth muscle cells, such as the SM1 and SM2 isoforms of smooth muscle myosin heavy

chain (Frangogiannis *et al.,* 2000b). Infarct myofibroblasts are predominantly derived from epicardium-derived fibroblast populations (Ruiz-Villalba *et al.,* 2015; Kanisicak *et al.,* 2016). During the proliferative phase of cardiac repair, suppression of pro-inflammatory signals, activation of TGF-β cascades and deposition of specialized matrix proteins, such as ED-A **fibronectin** (Arslan *et al.,* 2011b) and matricellular proteins (Frangogiannis, 2017a), trigger conversion of interstitial fibroblasts into myofibroblasts.

Activated myofibroblasts have been identified as the main source of ECM proteins in the healing infarct (Cleutjens *et al.,* 1995). In addition to their matrix synthetic capacity, activated infarct fibroblasts may also contribute to phagocytosis of dead cells (Nakaya *et al.,* 2017) and may secrete mediators that modulate cardiomyocyte survival (Abrial *et al.,* 2014) or mediate activation of immune cells (Anzai *et al.,* 2017). Whether distinct subpopulations are responsible for the functional pleiotropy of infarct myofibroblasts remains unknown. Excessive fibroblast activation may lead to expansion of the fibrotic area, increasing myocardial stiffness and promoting diastolic dysfunction. The potential involvement of negative regulatory mechanisms that restrain fibrogenic signals, in the prevention of uncontrolled fibrosis following MI, has not been investigated.

Inflammation in the remodelling myocardium

In the presence of a large infarction, massive loss of contractile myocardium is associated with activation of an inflammatory response in remote remodelling myocardial segments, accompanied by progressive interstitial fibrosis (Sager *et al.,* 2016b). Several mechanisms may contribute to inflammatory activation in the remodelling myocardium. First, volume and pressure loads, related to dilation of the chamber following infarction and to the elevation of filling pressures. Mechanical stress in the remodelling myocardium may locally activate macrophages stimulating their proliferation and promoting a fibrogenic environment (Sager *et al.,* 2016b). Second, defective suppression or impaired spatial containment of the inflammatory response in the infarct border zone may lead to prolonged activation of inflammatory pathways or expansion of the inflammatory infiltrate to viable segments (Frangogiannis *et al.,* 2005). Third, an immune-mediated response triggered by poorly defined antigens may mediate chronic inflammation in the remodelling myocardium (Ismahil *et al.,* 2014). In human ischaemic heart failure, subpopulations of patients may exhibit dysregulated inflammatory responses that may contribute to the pathogenesis of the cardiomyopathy.

The rationale for targeting inflammation after MI

The critical role of inflammation in all aspects of the myocardial response to injury suggests that targeting inflammatory signals may hold promise to reduce mortality and prevent heart failure in patients surviving an acute MI. The cell biological basis supporting therapeutic interventions that modulate the post-MI inflammatory cascade may involve several distinct beneficial actions. First, attenuation of inflammation during the early post-ischaemic inflammatory phase may prevent leukocyte-mediated cardiomyocyte injury in surviving cardiomyocytes of the border zone. Second, inhibition of inappropriate late activation of pro-inflammatory signalling may protect cardiomyocytes in the remodelling area from chronic apoptosis. Third, attenuation of inflammation may restrain protease activation, increasing the tensile strength of the healing scar and preventing adverse remodelling. Fourth, suppression of inflammation-driven fibrogenic signalling may protect the heart from dysregulated fibrotic remodelling. Fifth, selective activation of chemokine-dependent recruitment of progenitor cells into the area of infarction may promote angiogenesis and even contribute to the ultimate goal of myocardial regeneration. Sixth, pro-inflammatory signalling has been linked to ventricular arrhythmias; thus, attenuation of inflammation may have direct anti-arrhythmic actions. Finally, anti-inflammatory approaches may prevent plaque rupture reducing the incidence of recurrent coronary events.

It should be emphasized that some of the protective effects of certain established therapeutic approaches in patients with MI, such as angiotensin converting enzyme inhibition (Leuschner *et al.,* 2010), angiotensin receptor blockade (Kohno *et al.,* 2008), mineralocorticoid receptor (MR) inhibition (Fraccarollo *et al.,* 2008), β-adrenoceptor blockade (Garcia-Prieto *et al.,* 2017) and administration of statins (Zhang *et al.,* 2005), may involve direct modulation of inflammation. For example, leukocyte-specific **β_2-adrenoceptor** signalling has been reported to mediate leukocyte recruitment in the infarcted heart (Grisanti *et al.,* 2016), and a recent study suggested that the infarct-limiting effects of β-blockade with metoprolol in a mouse model of MI were lost following neutrophil depletion or through genetic knockdown of genes associated with platelet:neutrophil interactions (Garcia-Prieto *et al.,* 2017). However, considering the broad effects of neurohumoral pathways on both cardiomyocyte and non-cardiomyocyte populations, the relative contribution of inflammatory cell modulation remains unclear.

Early attempts to inhibit inflammation were primarily focused on the use of broad anti-inflammatory strategies, such as glucocorticoids. These approaches were often associated with adverse consequences. Over the last 30 years, progress in fundamental immunology and better understanding of cardiac pathophysiology led to implementation of new therapeutic strategies targeting specific inflammatory pathways. Despite the increasing sophistication of the approaches, therapeutic implementation of inflammatory targets in patients with MI remains challenging, in part due to the remarkable pathophysiological heterogeneity of the human condition.

Broad anti-inflammatory interventions

Glucocorticoids

Due to the ubiquitous expression of the **glucocorticoid receptor (GR)** in all nucleated cells, glucocorticoids have a wide range of effects on many different cell types and are

potent regulators of the inflammatory response (Cain and Cidlowski, 2017). During the alarm phase, glucocorticoids attenuate responses to danger signals, suppressing production of inflammatory mediators. Glucocorticoids also markedly reduce leukocyte infiltration into the tissues, by decreasing chemokine expression and by suppressing adhesive interactions between leukocytes and endothelial cells. During the resolution phase, glucocorticoids exert a wide range of actions on both inflammatory and reparative cells. Glucocorticoids are known to promote clearance of apoptotic cells (Liu *et al.,* 1999) and direct macrophages towards an anti-inflammatory phenotype (Snyder and Unanue, 1982). In addition to their effects on immune cells, glucocorticoids also inhibit repair, by reducing fibroblast-derived collagen synthesis and by inhibiting the angiogenic response. It should be emphasized that the effects of glucocorticoids are not limited to activation of GR signalling. Glucocorticoids also bind with high affinity to the **MR**s (Arriza *et al.,* 1987) and may also act by activating transcription-independent non-classical pathways, involving cell surface receptors (Samarasinghe *et al.,* 2012). Stimulation of MR signalling mediates pro-inflammatory macrophage activation *in vitro* and *in vivo* (Usher *et al.,* 2010), whereas activation of endogenous myeloid cell-specific GR signalling has been suggested to mediate reparative pathways (Galuppo *et al.,* 2017). The relative role of GR and MR activation in the response to glucocorticoid treatment is likely to depend on the specific agent used, the dose and on the cell biological context.

Numerous experimental studies have examined the effects of glucocorticoids in experimental models of MI (Table 1). Unfortunately, most of the studies were performed in models of non-reperfused MI, limiting the value of the conclusions in the current era of myocardial reperfusion. Although the effects are dependent on the agent used, the dose and duration of treatment, several studies have suggested that glucocorticoids may protect the infarcted myocardium, reducing cardiomyocyte necrosis and apoptosis (Libby *et al.,* 1973; Xu *et al.,* 2011). The basis for these protective actions is unclear, especially considering the use of permanent coronary occlusion models that would be expected to cause death of most cardiomyocytes in the area at risk. Other *in vivo* studies suggested that high-dose corticosteroid therapy impairs clearance of dead cells from the infarct and may disrupt fibroblast function (Kloner *et al.,* 1978), leading to formation of thinner scars. These effects would be expected to be detrimental in repair of the infarcted heart and may precipitate adverse remodelling. Clinical studies on the use of corticosteroids in patients with MI have produced conflicting results (Table 2). Although some studies reported protective effects, in other studies, significant concerns were raised regarding the safety of the approach (Roberts *et al.,* 1976; Giugliano *et al.,* 2003). Considering their broad actions on all cell types involved in cardiac injury and repair and their effects on several molecular cascades, glucocorticoids cause a wide range of adverse effects and are unattractive therapeutic options for patients with MI. However, understanding the cell-specific actions of GR activation may suggest more targeted approaches with therapeutic potential. Moreover, recent insights into the pathways involved in tissue-specific intracellular metabolism of glucocorticoids have suggested novel therapeutic directions (Gray *et al.,* 2017). The enzyme **11-β hydroxysteroid dehydrogenase (11-β-HSD)** catalyses intracellular regeneration of glucocorticoids from inert metabolites. In a mouse model, global deletion of 11-β-HSD1, the more widely distributed isoform of the enzyme, promoted angiogenesis and attenuated infarct expansion following MI (White *et al.,* 2016), suggesting that endogenous glucocorticoid regeneration may inhibit repair and exacerbate remodelling following MI. Thus, approaches inhibiting 11-β-HSD1 may be of therapeutic value to prevent development of heart failure following MI.

Nonsteroidal anti-inflammatory drugs (NSAIDs)

NSAIDs (including aspirin) have broad anti-inflammatory actions as their effects are mediated through inhibition of **COX**, the rate limiting enzyme in prostaglandin synthesis. There are two major isoforms of COX, the constitutively expressed COX-1 and COX-2, which is not found in normal tissues but is induced by inflammation, ischaemia and stress. Non-selective NSAIDs, introduced in the 1950s, inhibit both COX isoforms. Inhibition of COX-1-induced prostaglandins in the gastric mucosa by traditional NSAIDs is often associated with gastrointestinal toxicity, including peptic ulcer disease. Thus, selective COX-2 inhibitors were introduced in the late 1990s in an attempt to develop anti-inflammatory strategies without the risk of gastrointestinal side effects (Boulakh and Gislason, 2016).

Aspirin acts through non-competitive, irreversible acetylation of COX. In nucleated cells, the ability of the cells to synthesize COX-1 and COX-2 *de novo* allows recovery of prostaglandin synthesis despite inhibition by aspirin. In contrast, in platelets, **thromboxane A_2** production is dependent on preformed COX-1. Thus, irreversible binding of aspirin to platelet COX-1 results in inhibition of platelet aggregation for the entire life of the platelet and mediates aspirin's potent cardioprotective actions by reducing the incidence of new cardiovascular events (ISIS-2 Collaborative Group, 1988). In contrast, because the NSAIDs, apart from aspirin, competitively and reversibly inhibit COX, they do not cause sustained inhibition of platelet aggregation and do not provide long-term protection from atherothrombotic cardiovascular events (Vonkeman and van de Laar, 2010).

Although some early studies in animal models suggested that both non-selective non-aspirin NSAIDs and selective COX-2 inhibitors may have protective effects following MI (Lefer and Polansky, 1979), by attenuating adverse remodelling, by reducing cardiomyocyte apoptosis and by increasing arteriolar density (Abbate *et al.,* 2006; Straino *et al.,* 2007), other experimental studies demonstrated detrimental effects on infarct healing, resulting in scar thinning (Brown Jr *et al.,* 1983; Hammerman *et al.,* 1984a; Hammerman *et al.,* 1983b) and accentuated systolic dysfunction (Table 3) (Timmers *et al.,* 2007). Moreover, genetic loss-of-function studies demonstrated protective effects for endogenous COX-2 in myocardial ischaemia/reperfusion models (Camitta *et al.,* 2001; Bolli *et al.,* 2002).

In the clinical setting, a large body of evidence suggests that exposure to NSAIDs increases risk of cardiovascular events in patients with known cardiovascular disease. In post-MI patients, administration of NSAIDs is associated with

Table 1

Effects of glucocorticoids in experimental models of MI

Model	Animal	Agent, dose and duration of treatment	Major findings	Ref.
Non-reperfused MI	Cat	**Methylprednisolone** (MP, 30 mg·kg^{-1}, i.v.) 30 min prior or 60 min following occlusion	Both pretreatment and post-occlusion administration reduced myocardial injury, assessed through reduction of ST segment elevation.	(Spath Jr *et al.*, 1974)
Non-reperfused MI	Dog	Group1: **Hydrocortisone** (HC, 50 mg·kg^{-1}, i.v.) 30 min after occlusion, followed by supplementary dose of 25 mg·kg^{-1} 12 h after occlusion; Group2: HC (50 mg·kg^{-1}, i.v.) 6 h after occlusion, followed by supplementary dose of 25 mg·kg^{-1} 12 h after occlusion	HC reduced infarct size and attenuated cardiomyocyte necrosis, even when administered 6 h after occlusion.	(Libby *et al.*, 1973)
Non-reperfused MI	Rat	MP (50 mg·kg^{-1} i.v.) 5 min after occlusion, followed by (50 mg·kg^{-1} i.m.) 3, 6 and 24 h after occlusion	MP treatment was associated with reduced collagen deposition, delayed inflammation and repair, and persistent presence of 'mummified' cardiomyocytes (cells with preservation of striations and sarcolemmal membrane that exhibited nuclear degeneration).	(Kloner *et al.*, 1978)
Non-reperfused MI	Rat	1. HC: 50 mg·kg^{-1} i.v. 5 min after occlusion; 2. Single-dose MP: 50 mg·kg^{-1} i.v. 5 min after occlusion; 3. Multiple dose MP: 50 mg·kg^{-1} i.v. 5 min after occlusion, followed by 50 mg·kg^{-1} i.m. at 3, 6 and 24 h	1. Based on histological analysis and measurements of creatine kinase (CK) activity, glucocorticoids salvaged injured myocardium (by 15% in the HC group, 21% in MP single dose group, and 21% in the MP multiple dose group. 2. Multiple dose MP caused infarct thinning	(Maclean *et al.*, 1978)
Non-reperfused MI	Cat	**Dexamethasone** (Dx), 8 mg·kg^{-1} i.v., 30 min prior to or 60 min following occlusion	1. Dx pre- or post- administration significantly attenuated the increase in plasma CPK activity. 2. Dx had no effects on the haemodynamic response within the first 5 h following MI.	(Spath and Lefer, 1975)
Non-reperfused MI	Dog	Group1: high dose MP (50 mg·kg^{-1} i.v). 15 min and 3, 24 and 48 h after occlusion; Group2: low dose MP (30 mg·kg^{-1} i.v). 15 min after occlusion	1. Low dose MP reduced the size of the infarct. 2. The high dose MP protocol (but not low dose MP) caused infarct thinning and worsened systolic dysfunction without affecting collagen content.	(Hammerman *et al.*, 1983a)
Non-reperfused MI	Dog	MP, 7.5 mg·kg^{-1}, i.v. twice daily for 7 days after occlusion	MP reduced infarct size and attenuated compensatory hypertrophy without affecting haemodynamics.	(Slutsky and Murray, 1985)
Non-reperfused MI	Rat	MP (50 mg·kg^{-1}, i.v.) immediately after occlusion, followed by 50 mg·kg^{-1}, i.p., q6 h for 3 days	MP decreased collagen content in the infarcted heart.	(Vivaldi *et al.*, 1987)

continues

Table 1
(Continued)

Model	Animal	Agent, dose and duration of treatment	Major findings	Ref.
Non-reperfused MI	Mouse	Dx (20 mg·kg^{-1}, i.p.) 20 h prior to occlusion	Dx treatment reduced infarct size, attenuating cardiomyocyte apoptosis.	(Xu *et al.*, 2011)
Non-reperfused MI	Rat	MP (5 mg·kg^{-1}, i.p.) starting 7 days post-MI and continued to 21 day after occlusion	MP did not affect mortality or infarct size, but attenuated hypertrophic remodelling and significantly increased capillary density.	(Van Kerckhoven *et al.*, 2004)
Reperfused MI	Dog	MP single dose (50 mg·kg^{-1}, i.v.) after occlusion	MP did not affect infarct size and haemodynamic variables.	(Genth *et al.*, 1982)
Reperfused MI	Dog	MP (30 mg·kg^{-1}, i.v.) after occlusion;	MP increased myocardial blood flow during ischaemia, but had no effect on blood flow after reperfusion.	(da-Luz *et al.*, 1982)
Ischaemia and reperfusion *in vivo*	Rabbit	low dose **prednisolone** (5 mg·kg^{-1}/24 h i.m.) or high dose prednisolone (10 mg·kg^{-1} /24 h i.m.) protocols	Infarct healing was significantly delayed in both low and high dose groups. However, infarct thinning was not affected.	(Shizukuda *et al.*, 1991)

a high risk of death and reinfarction and an increased risk of hospitalization due to heart failure (Gislason *et al.*, 2006; Brophy *et al.*, 2007). Several mechanisms may explain the detrimental effects of NSAIDs in patients with MI. First, COX-2 inhibition may promote pro-thrombotic events by inhibiting generation of **prostacyclin**. Second, loss of renal actions of COX-2 may elevate blood pressure and promote heart failure decompensation. Third, COX-2 inhibition may block atheroprotective actions, thus accelerating atherosclerosis (Egan *et al.*, 2004). Fourth, COX-2 targeting may inhibit important cardioprotective actions and exert pro-arrhythmic effects. Fifth, COX inhibition may disrupt important reparative functions, leading to formation of a defective scar (Hammerman *et al.*, 1984b). Considering the abundant clinical evidence suggesting detrimental effects, all non-aspirin NSAIDs should be avoided in patients with established cardiovascular disease (Schmidt *et al.*, 2016).

Immunomodulatory strategies

Few studies have tested the effects of non-specific immunomodulation and immunosuppression in MI. In animal models, early administration of low-dose immunosuppressive agents has been reported to exert beneficial actions. However, clinical studies have provided disappointing results. In a rat model of reperfused MI, **cyclophosphamide** administration attenuated leukocyte infiltration and reduced ventricular dysfunction (Zhu *et al.*, 2008). **Methotrexate** treatment was also found to exert protective effects on the ischaemic and reperfused myocardium in both large animal (Asanuma *et al.*, 2004) and rodent models (Maranhao *et al.*, 2017). However, in a small clinical trial, methotrexate administration to patients with STEMI did not affect acute infarct size and worsened systolic dysfunction 3 months after the acute event (Moreira *et al.*, 2017). Immune modulation with intravenous immunoglobulin also failed to reduce infarct size and attenuate adverse remodelling in STEMI patients (Gullestad *et al.*, 2013).

Cyclosporine, another potent immunosuppressive agent, has attracted interest as a therapeutic agent for patients with MI, because of its effects as a cyclophilin B inhibitor. It has been proposed that cyclophilin B inhibition may inhibit opening of the mitochondrial permeability transition pore, thus protecting ischaemic cardiomyocytes from death. In addition to its protective actions on cardiomyocytes, **cyclosporine** may also reduce inflammation in the infarcted heart (Squadrito *et al.*, 1999). Despite promising early results in pilot studies, suggesting reduced infarct size in STEMI patients treated with cyclosporine (Piot *et al.*, 2008), a large randomized double-blind controlled trial showed no beneficial effects of a bolus dose of cyclosporine in STEMI patients undergoing percutaneous coronary intervention (PCI) (Cung *et al.*, 2015).

The failures of broad anti-inflammatory inhibition with corticosteroids and NSAIDs and advances in understanding the biology of the inflammatory response led to the development of specific inflammatory targets following MI.

Targeted anti-inflammatory interventions

Experimental studies have identified crucial molecular signals mediating the inflammatory response following MI. Therapeutic interventions in animal models suggested that

Table 2

Effects of glucocorticoid treatment in patients with MI

Type of study	Number of patients	Agent, dose and duration	Major findings	Ref.
Double blind clinical trial	132	oral **prednisone** (starting dose: 30 mg·day^{-1}), for 12 days	No difference in acute mortality. No difference in rhythm and conduction disturbance, and cardiac rupture.	(Sievers *et al.*, 1964)
Prospective cohort study	446	Hydrocortisone (HC), 500 mg i.v. for the first 4 days	HC significantly reduced mortality. There were no differences in the incidence of acute complications (acute heart failure, shock, cardiac arrhythmia, infections).	(Barzilai *et al.*, 1972)
Prospective cohort study	39	Methylprednisolone (MP): 3 g, 7–12 h following rise of serum CPK	MP treatment reduced infarct size.	(Morrison *et al.*, 1975)
Prospective cohort study	66	MP (i.v.): 1. Single 2.0 g dose 7–25 h following initial rise of CPK; 2. Two 2.0 g doses, 3–12 h apart	Reduction of infarct size and mortality in both MP treatment groups.	(Morrison *et al.*, 1976)
Prospective cohort study	44	1. Single dose: MP, 30 mg·kg^{-1}, i.v., 7 h from first CPK elevation; 2. Multiple dose: MP, 30 mg·kg^{-1}, i.v. starting after 7 h from first CPK elevation, every 6 h, for 48 h	Neither single dose nor multiple dose affected haemodynamics. Multiple dose MP (but not single dose) extended infarct size, increased ventricular dysrhythmias, and caused hyperglycaemia.	(Roberts *et al.*, 1976)
Prospective cohort study	29	MP 30 mg·kg^{-1}, i.v. 7 h and 10 h from onset of symptoms	High doses of MP given early in the course of MI have neither deleterious nor beneficial effects.	(Peters *et al.*, 1978)
Prospective cohort study	10	MP, 2.0 g i.v. single dose, average of 13 h from onset of chest pain	MP administration had no short-term protective effects and worsened haemodynamics.	(Heikkila and Nieminen, 1978)
Prospective cohort study	45	Methylprednisolone, single dose 25 mg·kg^{-1}, i.v. within 4 h after onset of chest pain	MP delayed cardiomyocyte injury and may stabilize lysosomal membranes during acute myocardial ischaemia.	(Welman *et al.*, 1979)
Prospective cohort study	42	MP, 30 mg·kg^{-1}, i.v four doses, q6 h.	Early short-term high-dose MP had no effects on infarct size, dysrhythmias, complications, or left ventricular function 2 weeks after infarction.	(Bush *et al.*, 1980)
Prospective cohort study	28	MP (30 mg·kg^{-1}), i.v. two doses, 2.5 h apart	MP administration in AMI patients had no effect on survival, infarct size and metabolic parameters, but increased cardiac output and reduced systemic vascular resistance.	(Henning *et al.*, 1981)
Retrospective cohort study	1746	N/A	Previous or inpatient corticosteroid use did not affect the incidence of cardiac rupture, or non-rupture related mortality in MI patients.	(Dellborg *et al.*, 1985)

continues

Table 2
(Continued)

Type of study	Number of patients	Agent, dose and duration	Major findings	Ref.
Retrospective study	41	N/A	This uncontrolled retrospective study suggested that use of anti-inflammatory agents (glucocorticoids and NSAIDs) before and after MI may be associated with a high incidence of cardiac rupture.	(Silverman and Pfeifer, 1987)
Double blind, randomized trial (RCT)	1118	Group 1: early MP: 30 mg·kg^{-1}, i.v. within 6 h of chest pain; repeated administration 3 h later; Group 2: late MP (30 mg·kg^{-1}, i.v.) 6–12 h from onset of chest pain; repeated administration 3 h later	Late treatment (6–12 h) with MP reduced mortality without affecting cardiac rupture, early malignant ventricular arrhythmias or other adverse cardiac events. Late MP treatment reduced 28 day and 6 month mortality in patients with inferior/posterior infarction, but not in anterior MI. Early treatment had no effects.	(Metz *et al.,* 1986) (The Solu-Medrol Sterile Powder AMI Study Group, 1986)
RCT	40	MP, 2.0 g, i.v. within 6 h, repeated same dose 3 h later	MP infusion had no effects on mortality, death from cardiac rupture, peak cardiac injury enzymes, arrhythmias, haemodynamics and 6 months hospitalization rates.	(Madias and Hood Jr, 1982)

targeted inhibition of specific inflammatory signals may protect the infarcted heart from acute injury and prevent adverse remodelling following MI. Despite promising results in animal models, therapeutic implementation of inflammatory targets in patients with MI has been challenging (Table 4).

Targeting the complement cascade

Activation of the complement cascade is a critical part of the innate immune response following MI and has been suggested to extend ischaemic injury (Yasojima *et al.,* 1998). In experimental studies, complement inhibition strategies have consistently reduced the size of the infarct and improved function in both rodent and large animal models of reperfused MI (Vakeva *et al.,* 1998; Pischke *et al.,* 2017). Unfortunately, clinical studies have been disappointing. Approaches targeting the complement system, an upstream activator of the innate immune response, were equally disappointing. In the Assessment of Pexelizumab in Acute Myocardial infarction clinical trial, treatment of STEMI patients with the anti-**C5** antibody pexelizumab did not affect 30 day mortality and the composite endpoint of death, cardiogenic shock and congestive heart failure (Armstrong *et al.,* 2007).

Targeting C-reactive protein (CRP)

Inflammatory injury is associated with release of **pentraxins** (such as CRP), prototypical acute phase proteins involved in host defense (Deban *et al.,* 2011). In an experimental model of non-reperfused infarction, CRP injection accentuated cardiomyocyte injury by activating the complement cascade, whereas (somewhat predictably) administration of low MW inhibitors of CRP blocked the deleterious effects of CRP (Pepys *et al.,* 2006). Despite these early promising findings, enthusiasm regarding the potential value of CRP inhibition in patients with MI is dampened by conflicting findings on the effects of CRP in atherosclerosis and thrombosis. Although, in apolipoprotein-E null mice, treatment with human native CRP accelerated atherosclerotic disease (Schwedler *et al.,* 2005), in other studies, transgenic overexpression of human CRP had no effects on atherosclerosis, thrombosis and inflammation (Hirschfield *et al.,* 2005; Tennent *et al.,* 2008) or even delayed plaque formation (Kovacs *et al.,* 2007). The conflicting *in vivo* effects of CRP may be explained by the contextually regulated formation of CRP isoforms with distinct functional properties. CRP is known to undergo dissociation from a native pentameric form (pCRP) to potently pro-inflammatory monomeric subunits (mCRP) that may serve to localize the inflammatory response (Eisenhardt *et al.,* 2009). Inhibition of CRP dissociation has been suggested as a promising anti-inflammatory strategy in MI.

Integrins and selectins

Selectins and leukocyte **integrins** are critically implicated in leukocyte extravasation in the infarcted myocardium (Figure 1). Numerous experimental studies demonstrated that neutralizing antibodies targeting members of the integrin and selectin families reduced the size of the infarct in myocardial ischaemia/reperfusion models (Simpson *et al.,* 1988; Ma *et al.,* 1991; Aversano *et al.,* 1995; Arai *et al.,* 1996; Christia and Frangogiannis, 2013). More recently, a

Table 3

Effects of NSAIDs in experimental models of MI

Model	Species	Agents dose duration delivery method	Major findings	Ref.
Reperfused MI	Dog	Group1: BW755C (inhibitor of both lipoxygenase and COX, 10 mg·kg^{-1}, i.v.) 30 min after reperfusion Group2: **Indomethacin** (5 mg·kg^{-1}, i.v.) 10 min before reperfusion	BW755C treatment reduced infarct size and decreased the incidence of arrhythmias, attenuating leukocyte infiltration. Treatment with indomethacin did not affect infarct size and leukocyte migration into the ischaemic myocardium.	(Mullane *et al.*, 1984)
Non reperfused MI	Dog	Indomethacin (10 mg·kg^{-1}, i.v.) at 15 min and 3 h after occlusion	Indomethacin caused infarct expansion and scar thinning.	(Hammerman *et al.*, 1984b)
Non reperfused MI	Cat	**Ibuprofen** (12.5 mg·kg^{-1}, i.v.) 0 and 2.5 h after occlusion	Ibuprofen attenuated myocardial injury without affecting haemodynamics during the early stage of infarction.	(Lefer and Polansky, 1979)
Non reperfused MI	Rat	**Aspirin** (25 mg·kg^{-1}·day^{-1}, i.p.) 2 days before occlusion until the end of the experiment	Aspirin significantly attenuated interstitial and perivascular fibrosis in the spared myocardium, without affecting wound healing, compensatory hypertrophy and LV dysfunction.	(Kalkman *et al.*, 1995)
Non reperfused MI	Mouse	Aspirin (120 mg·kg^{-1}·day^{-1}, subcutaneously) after occlusion for 4 weeks	High dose aspirin did not affect post-infarct cardiac remodelling and cardiac dysfunction, but attenuated pro-inflammatory cytokine levels.	(Adamek *et al.*, 2007)
Non-reperfused MI	Pig	**Celecoxib** (COX-2i; 400 mg p.o. bid) after occlusion until end of protocol	Celecoxib increased mortality, promoted infarct thinning, LV dilatation, and accentuated systolic dysfunction.	(Timmers *et al.*, 2007)
Non-reperfused MI	Rat	**Parecoxib** (COX-2i, 0.75 mg·kg^{-1} i.p.) 24 h after occlusion, daily for 5 days	Parecoxib ameliorated remodelling, reducing peri-infarct apoptosis and preserving arteriolar density. Parecoxib did not affect mortality, infarct size and plasma inflammatory cytokines.	(Straino *et al.*, 2007)
Non-reperfused MI	Mouse	Parecoxib (COX-2i, 0.75 mg·kg^{-1}, i.p.) 24 h after surgery, daily for 5 days	Parecoxib treatment significantly reduced apoptosis in the peri-infarct region; No difference of mortality on day 7.	(Abbate *et al.*, 2006)
Reperfused and non-reperfused MI	Mouse	Parecoxib (COX2i, 0.75 mg·kg^{-1}·day^{-1}, i.p.) for 7 days	Parecoxib treatment reduced mortality and attenuated apoptosis in non-reperfused infarcts, but had no effects in reperfused infarction.	(Salloum *et al.*, 2009)

continues

Table 3
(Continued)

Model	Species	Agents dose duration delivery method	Major findings	Ref.
Non-reperfused MI	Rat	Group 1: DFU (COX2i, 5 mg·kg^{-1}·day^{-1}, p.o.); Group 2: low dose aspirin (1 mg·kg^{-1}·day^{-1}, p.o.); Group 3: high dose aspirin (25 mg·kg^{-1}·day^{-1}, p.o.) 30 min prior to occlusion for 3 months	DFU treatment significantly reduced left ventricular end-diastolic pressure, reduced infarct size and improved cardiac contractility without affecting mortality. Aspirin had no effects on cardiac function.	(Saito *et al.,* 2004)
Non-reperfused MI	Mouse	NS-398 (COX-2i, 3 mg·kg^{-1}·day^{-1}, p.o.) 48 h after occlusion for 2 weeks; Rofecoxib (COX2i, 15 mg·kg^{-1}·day^{-1}, p.o.), 48 h after occlusion for 2 weeks	NS-398 attenuated adverse remodelling and dysfunction following MI without affecting infarct size. Both COX2i reduced cardiac hypertrophy, collagen production, and TGF-β expression in the infarcted heart.	(LaPointe *et al.,* 2004)
Non-reperfused MI	Dog	**Piroxicam**, (1 mg·kg^{-1} i.v.) 15 min, 3 h after occlusion	Piroxicam caused moderate scar thinning without perturbing regional function.	(Hammerman *et al.,* 1984a)

nanoparticle-based strategy silencing five key adhesion molecules was reported to preserve function in the infarcted myocardium (Sager *et al.,* 2016a). Protection of the myocardium was presumably due to attenuation of leukocyte-mediated cardiomyocyte injury. Unfortunately, clinical trials did not confirm the impressive protective effects of anti-adhesion molecule approaches observed in experimental studies. Anti-**CD11**/**CD18** and anti-CD18 integrin targeting failed to reduce infarct size in STEMI patients (Baran *et al.,* 2001; Rusnak *et al.,* 2001; Faxon *et al.,* 2002) (Table 4). On the other hand, administration of the P-selectin inhibitor inclacumab in patients with ACS reduced cardiomyocyte injury but did not affect clinical outcome (Tardif *et al.,* 2013; Seropian *et al.,* 2014).

Chemokines as therapeutic targets

Approaches targeting chemokines involved in recruitment of pro-inflammatory leukocytes have shown promising results in experimental animal models. Anti-CCL2 therapy reduced mortality, attenuated chamber dilation and improved systolic function in a model of non-reperfused infarction (Hayashidani *et al.,* 2003). Inhibition of **CCL5** also exerted protective effects, improving cardiac function and attenuating fibrotic remodelling (Montecucco *et al.,* 2012). Silencing the **chemokine receptor CCR2**, the main receptor for CCL2, that mediates recruitment of pro-inflammatory monocytes in sites of inflammation, was reported to have beneficial effects not only in the infarcted heart but also in the composition of atherosclerotic plaques and in metabolic dysfunction (Leuschner *et al.,* 2011). However, it should be emphasized that broad targeting of the effects of CC chemokines may also have detrimental actions. Chemokine-mediated signalling is important for recruitment of leukocyte subsets with anti-inflammatory properties and may be involved in activation of a programme of repair. In a mouse model of reperfused MI, genetic disruption of **CCR5** was associated with accentuated dilative remodelling, presumably due to impaired recruitment of anti-inflammatory monocyte subsets and of Tregs (Dobaczewski *et al.,* 2010). Thus, recruitment of specific leukocyte subsets through chemokine-chemokine receptor interactions may be critical for repression and resolution of post-infarction inflammation.

Administration of the chemokines that recruit reparative cells, such as CXCL12, may also hold therapeutic promise. Therapy with CXCL12 reduced infarct size and accentuated angiogenesis in experimental models of MI, attenuating systolic dysfunction and improving left ventricular mechanics (Hu *et al.,* 2007; Saxena *et al.,* 2008; Macarthur Jr *et al.,* 2014; MacArthur Jr *et al.,* 2013). Although these experimental findings seem promising, clinical translation is challenging. Loss-of-function studies have suggested important pro-inflammatory actions of CXCL12 in the infarcted heart (Proulx *et al.,* 2007; Jujo *et al.,* 2010) raising concerns that administration of this chemokine may also have injurious effects, accentuating or prolonging inflammatory cascades. Clinical evidence remains extremely limited, as the effects of CXCL12 therapy in MI has not been studied. However, in a Phase II clinical trial in patients with high-risk ischaemic cardiomyopathy, CXCL12 gene therapy was safe but did not meet the primary endpoint for functional improvement (Chung *et al.,* 2015).

Targeting the cytokines

Although a growing body of experimental evidence suggests that pro-inflammatory cytokines may be promising therapeutic targets in patients with MI, their pleiotropic and multifunctional effects, and their involvement in both

Table 4

Targeted anti-inflammatory and immunomodulatory therapies in patients with MI

Type of study	Number of patients	Agent, dose and duration	Major findings	Ref.
Anti-integrin				
RCT: FESTIVAL	88	**Rovelizumab** (anti-CD11/18, also known as LeukArrest or Hu23F2G) Low dose: (0.3 mg·kg^{-1}) High dose: (1.0 mg·kg^{-1}) i.v. after coronary angiography	Hu23F2G was well tolerated, with no increase in adverse events, including infections. Single-photon emission computed tomographic (SPECT) imaging showed no significant effects of anti-CD11/CD18 treatment on myocardial infarct size in STEMI patients.	(Rusnak *et al.*, 2001)
RCT: HALT-MI	420	Rovelizumab (anti-CD11/18) Low dose: (0.3 mg·kg^{-1}) High dose: (1.0 mg·kg^{-1}) i.v. before coronary angioplasty	Treatment with anti-CD11/CD18 did not affect infarct size in STEMI patients who underwent primary angioplasty.	(Faxon *et al.*, 2002)
RCT: LIMIT-AMI	394	Anti-CD18 (i.v. bolus of 0.5 or 2.0 mg·kg^{-1}, before commencing recombinant tissue plasminogen activator (rtPA)	No significant effects on coronary blood flow, infarct size, or the rate of ECG ST-segment elevation resolution STEMI patients treated with rtPA.	(Baran *et al.*, 2001)
Anti-Selectin				
RCT: SELECT-ACS	544	Inclacumab (anti-P-Selectin), single infusion 5 or 20 mg·kg^{-1}, 1–12 h before PCI	Inclacumab at a dose of 20 mg·kg^{-1} appeared to reduce myocardial damage after PCI in non-STEMI patients, without significant difference in adverse events.	(Tardif *et al.*, 2013)
IL-1 inhibition				
Pilot Study: VCU-ART	10	Anakinra (IL-1RN) 100 mg·day^{-1} subcutaneously for 14 days	IL-1 blockade with anakinra was safe and ameliorated LV remodelling in STEMI patients.	(Abbate *et al.*, 2010)
Pilot Study: VCU-ART2	30	Anakinra (IL-1RN) 100 mg·day^{-1} subcutaneously for 14 days	Anakinra blunted the acute inflammatory response in STEMI patients, without showing benefits of LV remodelling or function.	(Abbate *et al.*, 2013)
RCT: MRC-ILA Heart Study	182	Anakinra (IL-1RN) 100 mg·day^{-1} subcutaneously for 14 days	Following 14 day treatment of IL-1RN, inflammatory markers were reduced; In patients with NSTE-ACS, IL-1RN treatment significantly increased major adverse cardiac events at 1 year, but not at day 30 or 3 months.	(Morton *et al.*, 2015)
RCT: CANTOS	10 061	Canakinumab (anti-IL-1β) at three different doses: 50, 150 and 300 mg	In patients with previous MI and an hs-CRP level ≥ 2 mg·L^{-1}, canakinumab (150 mg) significantly reduced hs-CRP,	(Ridker *et al.*, 2017)

continues

Table 4

(Continued)

Type of study	Number of patients	Agent, dose and duration	Major findings	Ref.
		subcutaneously, once every 3 months	but increased the incidence of fatal infection and sepsis. The 300 mg dose had similar effects, but the multiple statistical comparisons yielded non-significant differences in comparison to the placebo group. The reduced rate of recurrent cardiovascular events in treated patients was independent of lipid level lowering.	
Anti-complement				
Pilot study	31	Complement 1 inhibitor (loading dose 50 or 100 $U \cdot kg^{-1}$ 6 h after MI, followed by continuous infusion 1.25 or 2 $U \cdot kg^{-1} \cdot h^{-1}$ for 48 h)	In MI patients who received early thrombolytic therapy, C1 inhibitor treatment reduced troponin T and creatine kinase-MB levels, without causing adverse effects.	(de Zwaan *et al.*, 2002)
RCT: COMPLY	943	Pexelizumab (anti-C5) bolus (2 $mg \cdot kg^{-1}$), or pexelizumab bolus (2 $mg \cdot kg^{-1}$) followed by pexelizumab infusion (0.05 $mg \cdot kg^{-1} \cdot h^{-1}$) for 20 h	In STEMI patients receiving fibrinolysis, adjunct treatment with pexelizumab neither reduced infarct size nor improved clinical outcomes.	(Mahaffey *et al.*, 2003)
RCT: COMMA	960	Pexelizumab bolus (2 $mg \cdot kg^{-1}$), or pexelizumab bolus (2 $mg \cdot kg^{-1}$) followed by pexelizumab infusion (0.05 $mg \cdot kg^{-1} \cdot h^{-1}$) for 20 h	In STEMI patients undergoing PCI, adjunct treatment with pexelizumab had no measurable effect on infarct size or on the composite of 90 day death, new or worsening heart failure, shock and stroke. 90 day mortality was significantly reduced in pexelizumab bolus plus infusion.	(Granger *et al.*, 2003)
RCT: APEX-AMI	5745	Pexelizumab prior to PCI, i.v. bolus 2 $mg \cdot kg^{-1}$, followed by 0.05 $mg \cdot kg^{-1} \cdot h^{-1}$ infusion over the subsequent 24 h	In patients treated with primary PCI for STEMI, adjunct pexelizumab treatment showed no significant effect on mortality or the composite endpoint of death, cardiogenic shock, and heart failure at day 30 or day 90.	(Armstrong *et al.*, 2007)
IL-6 antagonism				
RCT	117	**Tocilizumab** (IL-6Ra, single dose 280 mg, i.v.) prior to coronary angiography	Tocilizumab attenuated the inflammatory response and PCI-related troponin T (TnT) release in NSTEMI patients. Tocilizumab did not affect coronary flow reserve during hospitalization or after 6 months.	PMID: (Kleveland *et al.*, 2016) (Holte *et al.*, 2017)

continues

Table 4
(Continued)

Type of study	Number of patients	Agent, dose and duration	Major findings	Ref.
TNF-α antagonism				
RCT	26	**Etanercept** (TNF-α antagonist) at a single intravenous dose of 10 mg	Following acute MI, etanercept reduced systemic inflammation but increased platelet activation without affecting peripheral vasomotor or fibrinolytic function.	(Padfield *et al.*, 2013)
Proteinase inhibition				
RCT: TIPTOP	429	Doxycycline (non-selective MMP inhibitor, 100 mg p.o.) immediately after primary PCI and then twice daily for 7 days	In patients with a first STEMI and LV dysfunction treated with primary PCI, a timely short-term treatment with doxycycline significantly reduced adverse LV remodelling and decreased infarct size assessed through SPECT.	(Cerisano *et al.*, 2014)
RCT: PREMIER	253	PG-116800 (MMP inhibitor), 200 mg oral dose taken twice daily for 90 days	MMPs inhibition with PG-116800 after MI failed to reduce LV remodelling or improve clinical outcomes in patients with STEMI.	(Hudson *et al.*, 2006)
Pilot clinical trial	10	**Prolastin C**, human plasma-derived **alpha1 antitrypsin (AAT)**, single infusion of 60 mg·kg^{-1}, within 12 h of revascularization	A single administration of Prolastin C in patients with STEMI is well tolerated and is associated with a blunted acute inflammatory response.	(Abbate *et al.*, 2015b)

injurious and reparative responses pose major therapeutic challenges. Recent experimental and clinical studies have suggested that the IL-1 system may represent a promising therapeutic target in patients with MI (Saxena *et al.*, 2016). Safe and effective strategies for IL-1 inhibition are extensively used treatment of patients with inflammatory arthritides or auto-inflammatory syndromes. Anakinra is a non-glycosylated recombinant form of **IL-1 receptor antagonist** that binds to the type I IL-1 receptor but does not activate a signalling response, thus functioning as a competitive IL-1α/IL-1β inhibitor. On the other hand, anti-IL-1β antibodies (such as **canakinumab**) selectively target IL-β-mediated responses. In most experimental MI studies, inhibition of the IL-1 system with anakinra or anti-IL-1β antibodies exerted protective effects, reducing chamber dilation and improving dysfunction (Abbate *et al.*, 2008; Toldo *et al.*, 2013). Early evidence from clinical studies has also produced promising results. Pilot studies demonstrated that **anakinra** can be safely administered as a 2 week course in STEMI patients and may attenuate adverse remodelling, while protecting from the development of post-infarction heart failure (Abbate *et al.*, 2010; Abbate *et al.*, 2013; Abbate *et al.*, 2015a). In the recently reported Canakinumab Antiinflammatory Thrombosis Outcome Study trial (Ridker *et al.*, 2017), IL-1β inhibition in high-risk patients with atherosclerotic disease attenuated inflammation and reduced cardiovascular events. In patients treated with 150 mg of canakinumab, the primary endpoint (the composite of MI, nonfatal stroke and cardiovascular death) was significantly lower. The beneficial effects of canakinumab were modest: to avoid one primary endpoint event, 156 patients had to be treated for 1 year. Moreover, the canakinumab group exhibited a very low, but significantly higher than placebo, death rate due to infection. Despite these issues and the concerns regarding the very high cost of the antibody, this landmark clinical trial supports the case for targeted anti-cytokine therapy in selected patients with MI. An emerging body of evidence suggesting that IL-1-mediated inflammation accentuates adverse remodelling post-MI (Bujak *et al.*, 2008) and may promote arrhythmia generation (Monnerat *et al.*, 2016; De Jesus *et al.*, 2017) further strengthens the rationale for targeting IL-1 in high-risk subpopulations of MI patients, suggesting that protection may not be limited to reduction of new atherothrombotic events.

The TGF-β system

Despite the critical involvement of **TGF-β** signalling in cardiac injury and repair (Frangogiannis, 2017b), targeting TGF-β following MI poses several major challenges. First, TGF-βs are known to modulate phenotype and function of

all cell types involved in cardiac injury and repair. Thus, TGF-β inhibition would be expected to affect both injurious and protective actions. The effects of TGF-β inhibition may be dependent on the timing of the intervention. Thus, early neutralization of TGF-β may block anti-inflammatory signalling in macrophages, accentuating inflammation and increasing the incidence of cardiac rupture, whereas late suppression may attenuate pro-fibrotic signals, improving diastolic function (Ikeuchi *et al.,* 2004). Second, because TGF-β is involved in preservation of cardiac and vascular homeostasis, TGF-β inhibition following MI may carry significant risks, promoting aneurysmal rupture in vulnerable patients (Engebretsen *et al.,* 2014; Frangogiannis, 2014b; Biernacka *et al.,* 2015). Third, the complex biology of TGF-β signalling further complicates design of therapeutic strategies. TGF-β signals through intracellular effectors, the Smads and through activation of non-Smad pathways (such as **p38 MAPK**, **Erk MAPK**, and **JNK**). Design of effective therapeutic strategies requires understanding of the relative role of Smad-dependent and Smad-independent signalling *in vivo* (Bujak *et al.,* 2007; Rainer *et al.,* 2014). In the infarcted heart, experimental studies have suggested distinct effects of Smad-dependent signalling in cardiomyocytes and fibroblasts (Kong *et al.,* 2017). Moreover, non-Smad pathways may also contribute to activation of interstitial cells towards a fibrogenic phenotype (Molkentin *et al.,* 2017). Dissection of cell-specific responses to TGF-β and understanding of the temporal sequence of its cellular actions in the infarcted heart are needed to design safe and effective therapeutic approaches.

Targeting the MMP system

MMPs are involved in post-MI repair and remodelling, not only by critically regulating ECM metabolism but also by processing inflammatory mediators, such as chemokines and cytokines (Fingleton, 2017; Frangogiannis, 2017a). Genetic deletion of MMP2 and MMP9 has been shown to attenuate post-MI ventricular dilation and to protect from cardiac rupture in mouse models of non-reperfused MI (Ducharme *et al.,* 2000; Matsumura *et al.,* 2005). However, pharmacological inhibition of MMPs in animal models of MI has produced conflicting results, depending on the timing of the intervention, the inhibition profile of the agent used and the experimental model. Early treatment with **doxycycline**, a non-selective MMP inhibitor, attenuated adverse remodelling in a rat model of non-reperfused infarction (Villarreal *et al.,* 2003). In contrast, early inhibition of MMP9 delayed resolution of inflammation and worsened dysfunction in a mouse model of permanent coronary occlusion (Iyer *et al.,* 2016). In clinical studies, no consistent beneficial effects of MMP inhibition have been reported. In the TIPTOP trial, administration of doxycycline (100 mg p.o. bid for 7 days) in patients with STEMI and left ventricular dysfunction reduced the size of the infarct and attenuated cardiac remodelling (Cerisano *et al.,* 2014). In contrast, in the PREMIER trial, administration of an MMP inhibitor with high affinity for MMP2, MMP3, MMP8, MMP9, MMP13 and MMP14 did not improve clinical outcomes and left ventricular remodelling in STEMI patients (Hudson *et al.,* 2006).

Challenges in targeting inflammation following MI

The diverse roles of inflammatory cascades in injury and repair

The critical involvement of inflammation in both injury and repair of the infarcted heart complicates attempts to target inflammatory signals in patients with MI (Saxena *et al.,* 2016). Inflammatory pathways have been implicated in extending cardiomyocyte death and in triggering matrix degradation but also play a critical role in clearance of dead cells from the infarct and in formation of a scar that preserves the structural integrity of the ventricle. Moreover, inflammatory mediators have been implicated in recruitment of progenitor cells involved in infarct angiogenesis (Taghavi and George, 2013). Thus, inhibition of an inflammatory signal involved in early injury may also inhibit a crucial repair response. Design of therapeutic strategies targeting inflammation in patients with MI needs to take into account important temporal and spatial considerations. There is ample evidence to suggest that prolonged or expanded pro-inflammatory signalling may accentuate adverse remodelling by activating proteases that degrade the cardiac ECM, by transducing pro-apoptotic responses in cardiomyocytes and by promoting fibrogenic signalling in the viable non-infarcted myocardium (Chen *et al.,* 2012; Frangogiannis *et al.,* 2005). It is likely that following MI, there is a therapeutic window of opportunity for safe and effective targeting of specific inflammatory signals. Understanding the time course of the cellular actions of specific inflammatory signals is critical for optimal design of therapeutic strategies.

The pathophysiological heterogeneity of human post-infarction remodelling

The remarkable pathophysiological heterogeneity in human patients surviving MI further complicates therapeutic implementation of promising targets. The extent of adverse post-MI remodelling is only partly dependent on the size of the infarct. Differences in susceptibility to adverse remodelling between patients may be explained by age and gender, genetic substrate, the presence or absence of concomitant conditions, the pattern of atherosclerotic disease, administration of medications and other poorly understood factors. Certain subpopulations of patients may have defective mechanisms for negative regulation of inflammation, thus exhibiting prolonged or expanded inflammatory responses. Others may have accentuated fibrotic reactions. Pathophysiological stratification of the patients on the basis of their biochemical profile, clinical characteristics and functional responses may identify patients with overactive post-infarction inflammatory responses that may benefit from targeted anti-inflammatory strategies (Frangogiannis, 2014a). Clinical and experimental studies suggest that certain patient subpopulations, such as diabetics, may exhibit dysregulated inflammatory reactions following MI that may be responsible for accentuated remodelling and worse dysfunction. Patients with diabetes have a high incidence of diastolic dysfunction following MI, despite a smaller infarct size and comparable systolic dysfunction (Stone *et al.,* 1989). In experimental models, diabetes and obesity are associated with

cardiomyocyte hypertrophy and interstitial fibrosis. These changes may reflect exaggerated angiotensin-mediated responses and increased TGF-β/Smad signalling (Biernacka *et al.,* 2015). Targeting fibrogenic mediators may be a promising therapeutic strategy in these patients. On the other hand, other patients may exhibit prolonged activation of pro-inflammatory signals. These patients may benefit from strategies targeting critical inflammatory cascades, such as IL-1. Biomarkers (Seropian *et al.,* 2016) and imaging approaches (Wollenweber *et al.,* 2014; Nahrendorf *et al.,* 2015) may be used to assess inflammatory activation in these patients, in order to design personalized therapeutic approaches.

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Harding *et al.,* 2018), and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18 (Alexander *et al.,* 2017a,b,c,d,e).

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Conflict of interest

The authors declare no conflicts of interest.

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